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Liu Research Group
April 25th, 2019

Total Synthesis of (–)-Mitrephorone A

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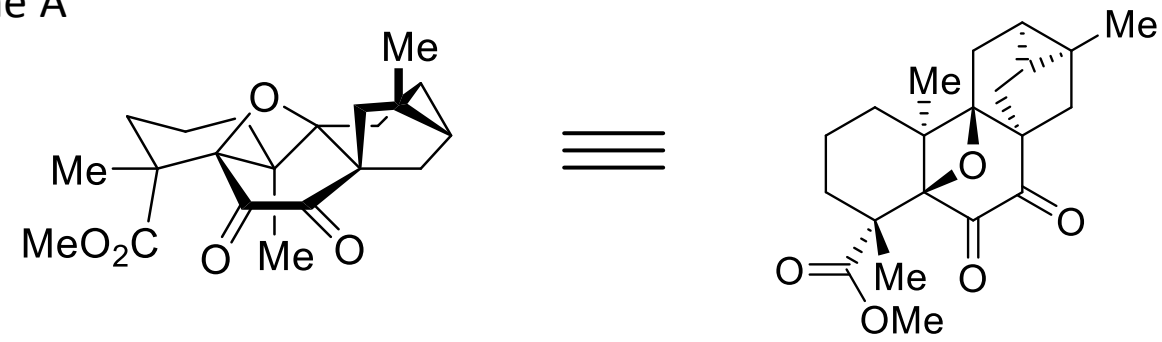
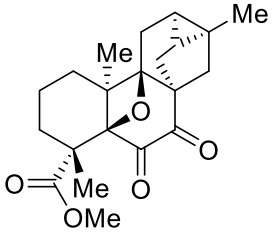
I. Introduction

- Isolated from the Bornean shrub *Mitrephora glabra* in 2005 by Oberlies and coworkers (Oberlies, *et. al. Org. Lett.* **2005**, *7*, 5709.)
- Exhibits antimicrobial activity and displays potent and broad cytotoxicity against various cancer cell lines
- Contains a fully substituted oxetane in a pentacyclic carbon skeleton
- Features a tetrasubstituted cyclopropane, four quaternary centers, and five contiguous stereocenters.
- First ever enantioselective synthesis of (-)-mitrephorone A

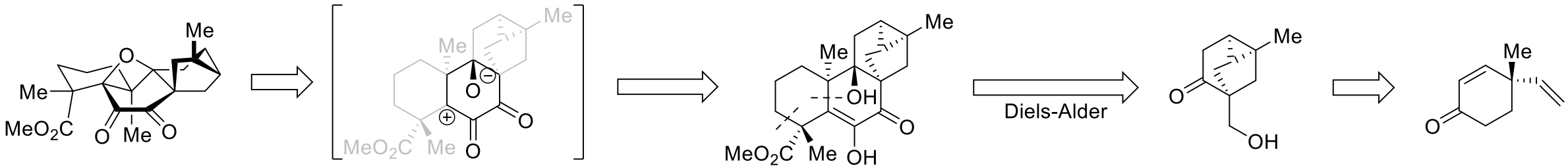


Carreira, *et. al. J. Am. Chem. Soc.* **2018**, *140*, 16704-16710.

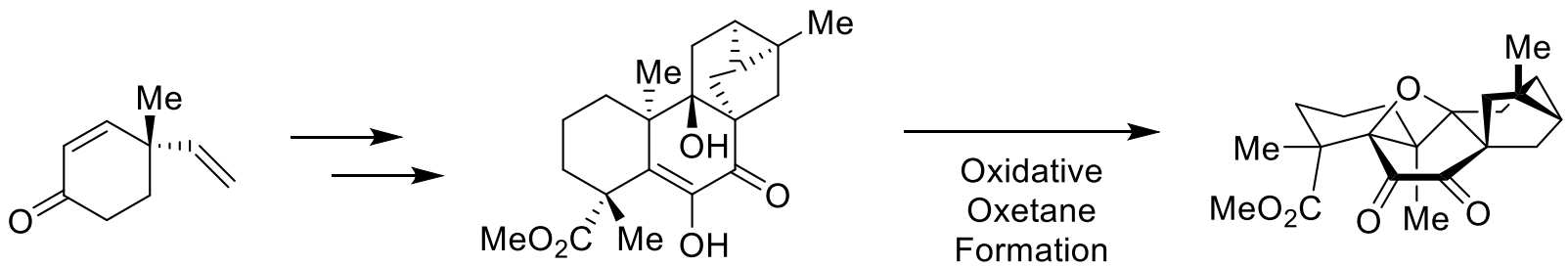
Goal:



II. Retrosynthesis



(-)-mitrephorone A | enolonium synthon | 2 | 3 | 4



4 | 2 | (-)-mitrephorone A

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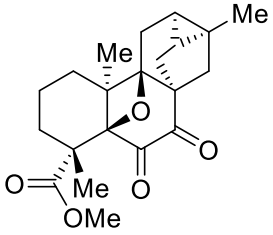
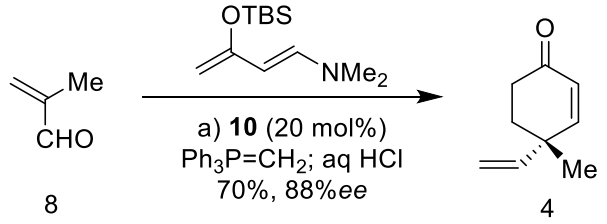


III. Construction of the Tricyclooctane Core



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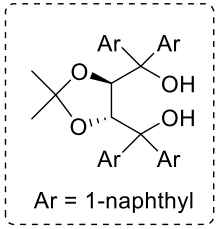
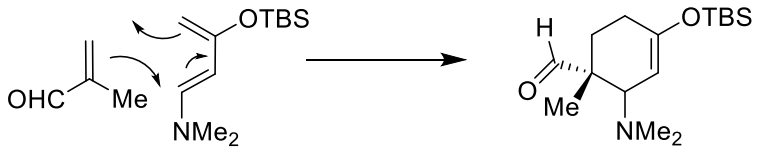
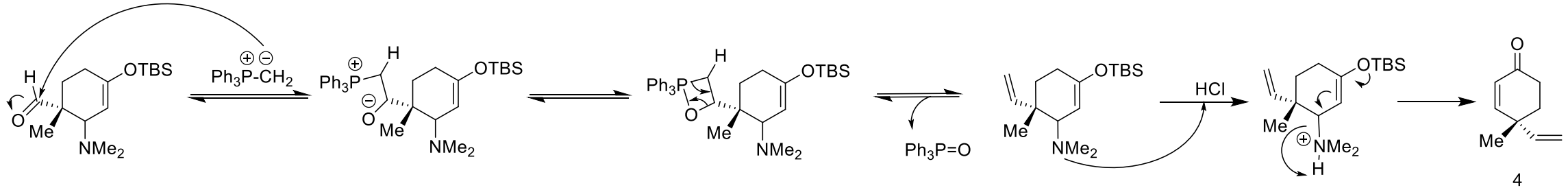


TADDOL-catalyzed Diels-Alder:



Wittig methenylation and acidic hydrolysis:



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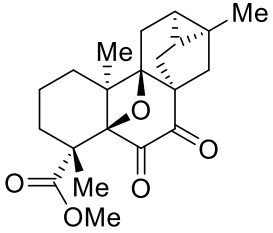

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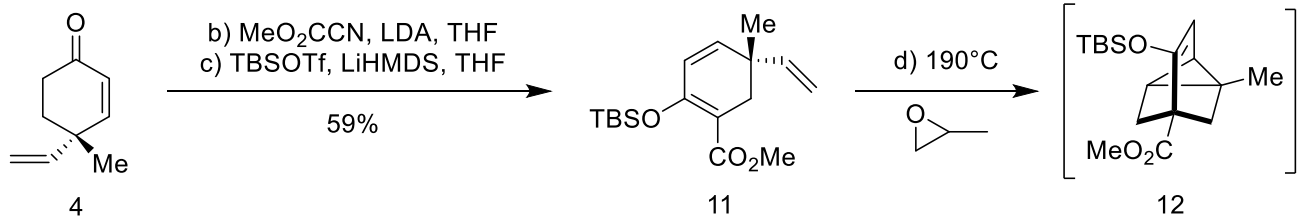
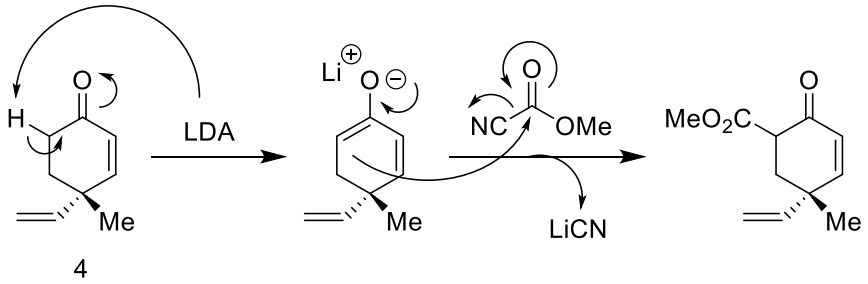


Introduction of methyl ester:



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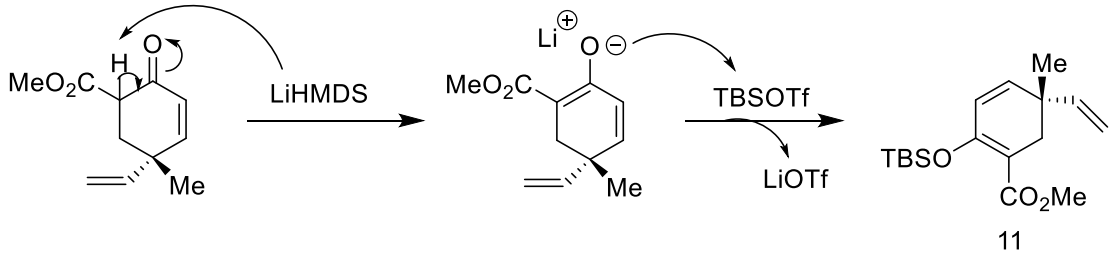

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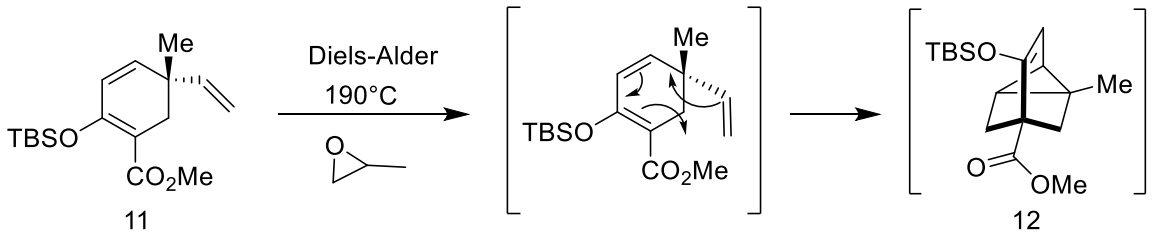

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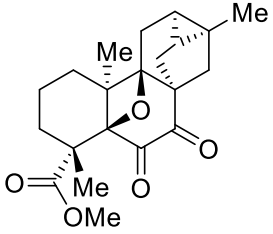
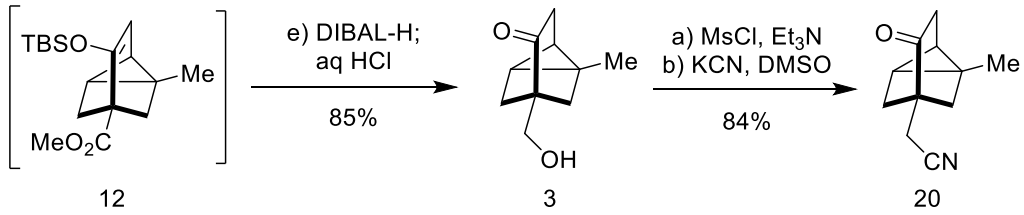


IV. Elaboration of the Tricyclooctane Core



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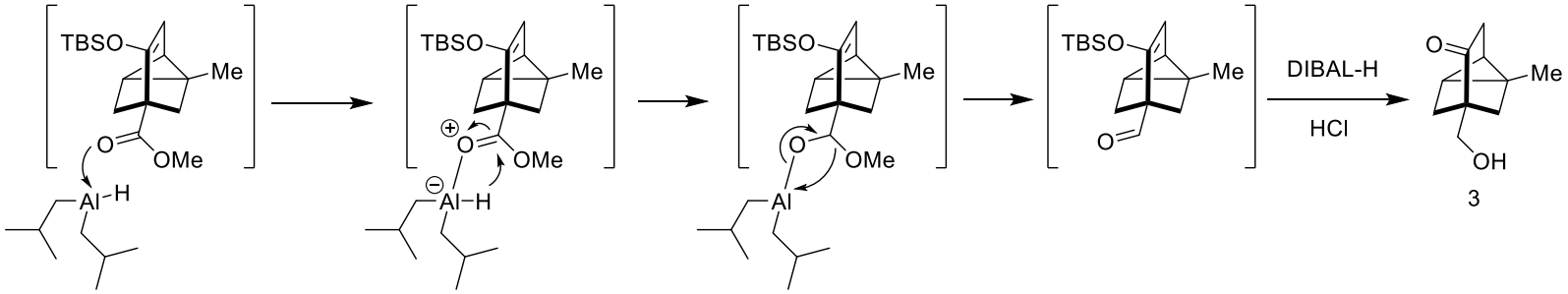
DIBAL reduction:



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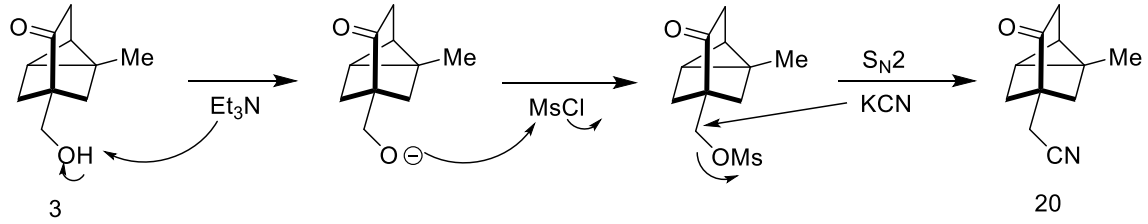
O-Mesylation and introduction of nitrile:



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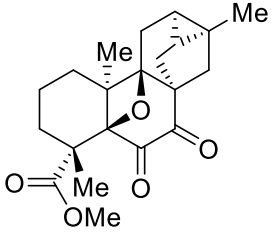

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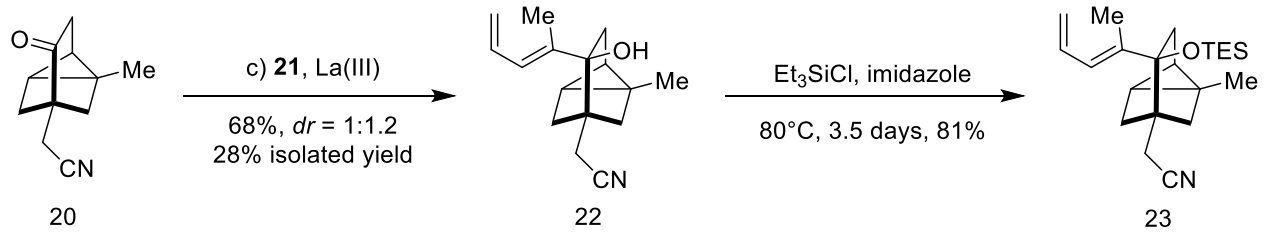
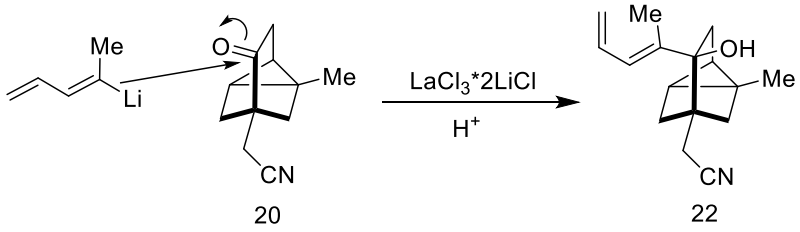


Introduction of 1,3-diene:



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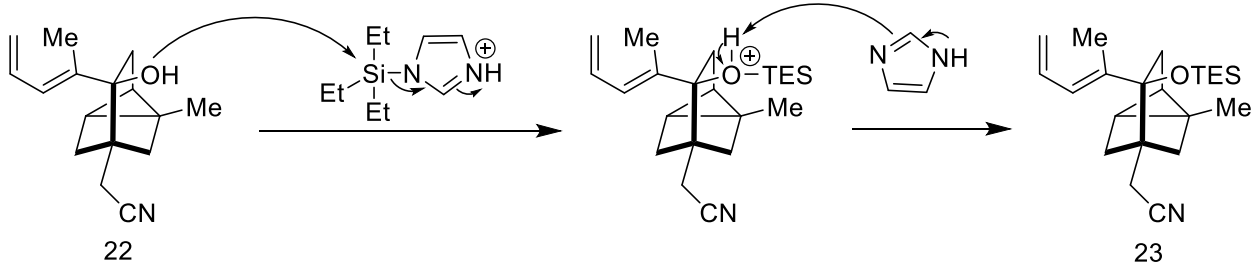

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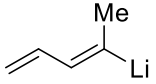

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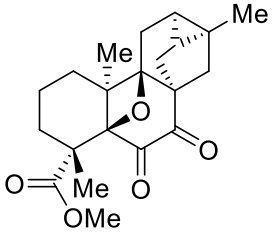
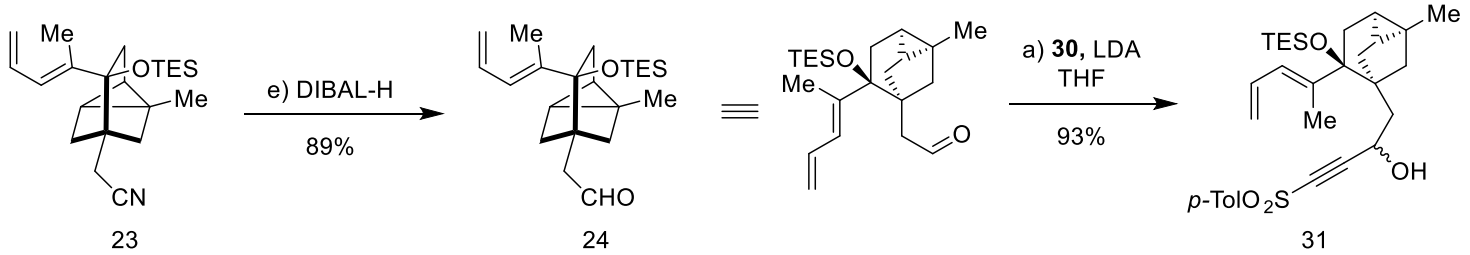
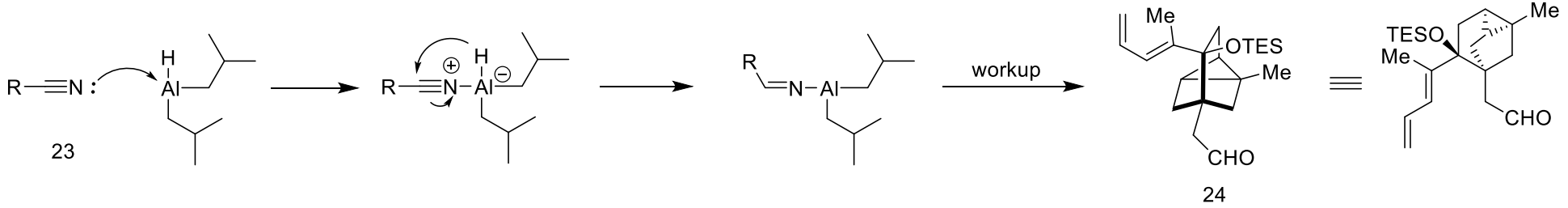


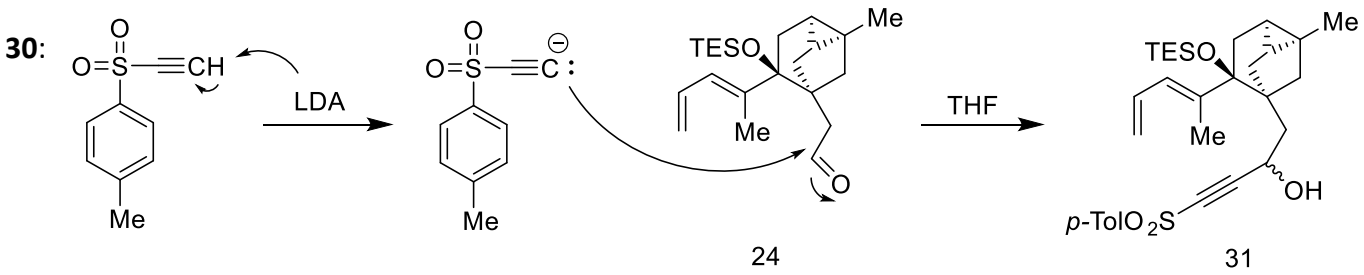
IV. Elaboration of the Tricyclooctane Core



DIBAL-H reduction of the nitrile:



Addition of ethynyl *p*-tolyl sulfone:



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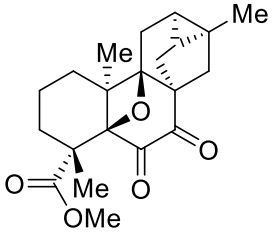
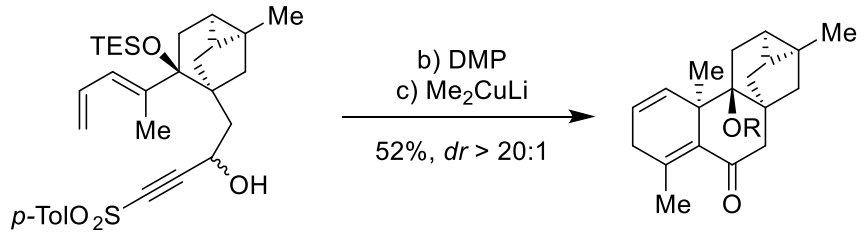


V. Construction of the Pentacyclic Framework



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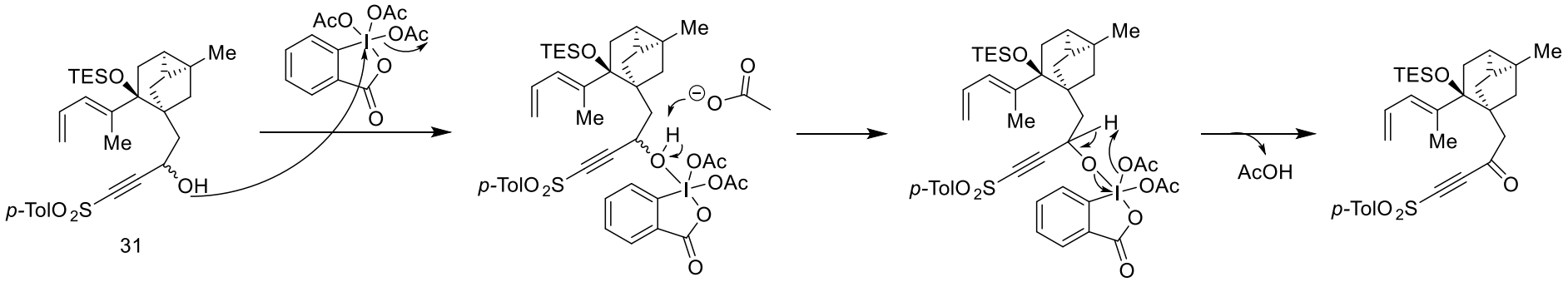
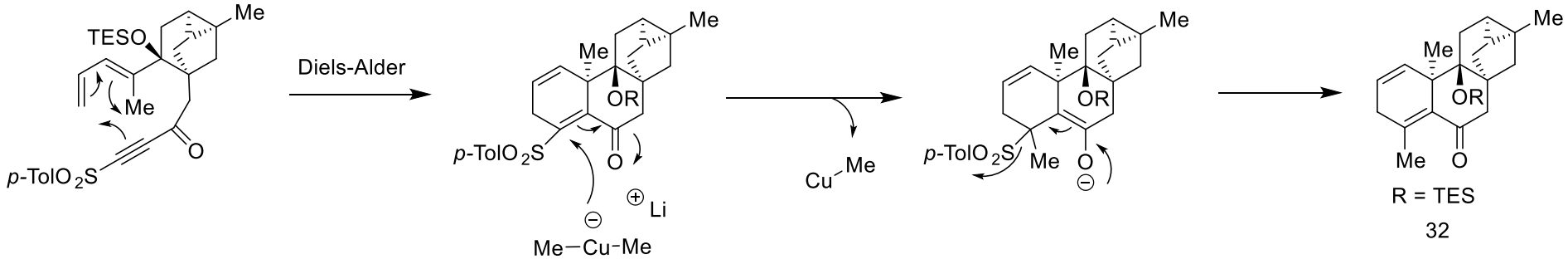
Dess-Martin Oxidation:



Conjugate addition and Diels-Alder:



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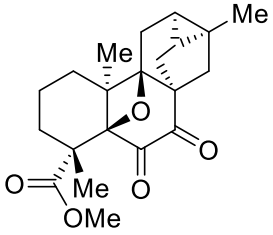

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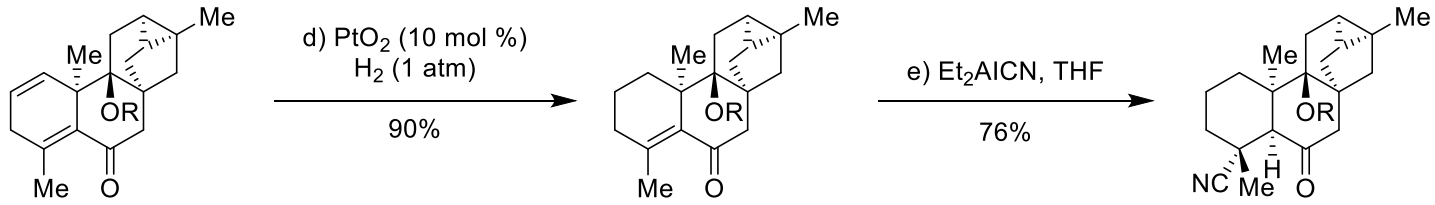
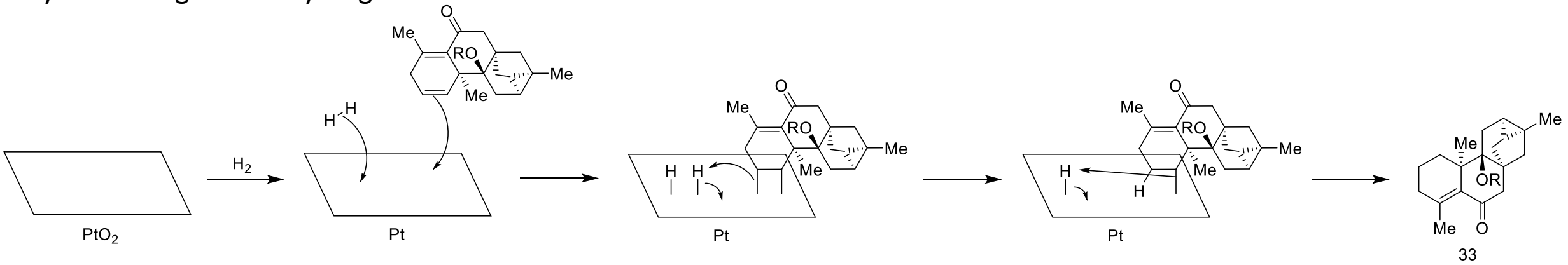
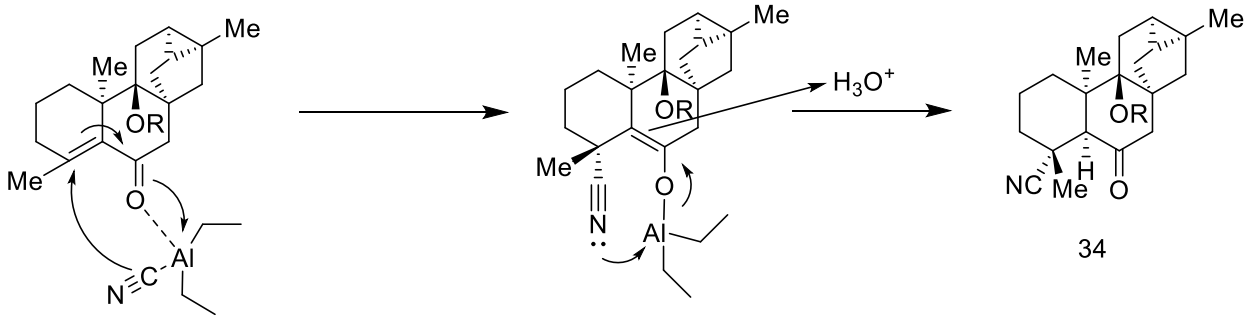


Catalytic heterogeneous hydrogenation:



Hydrocyanation:



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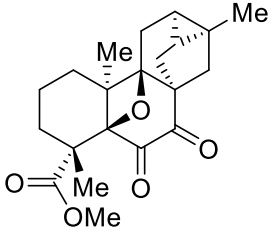

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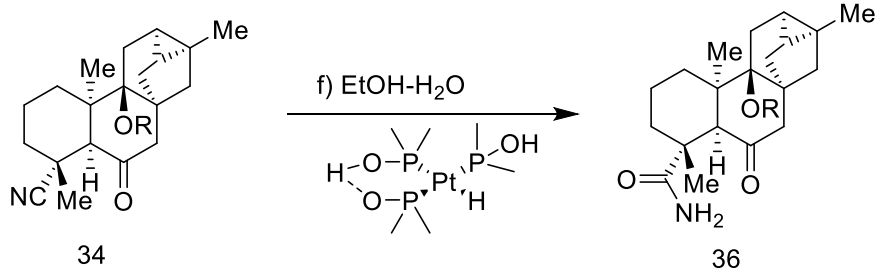
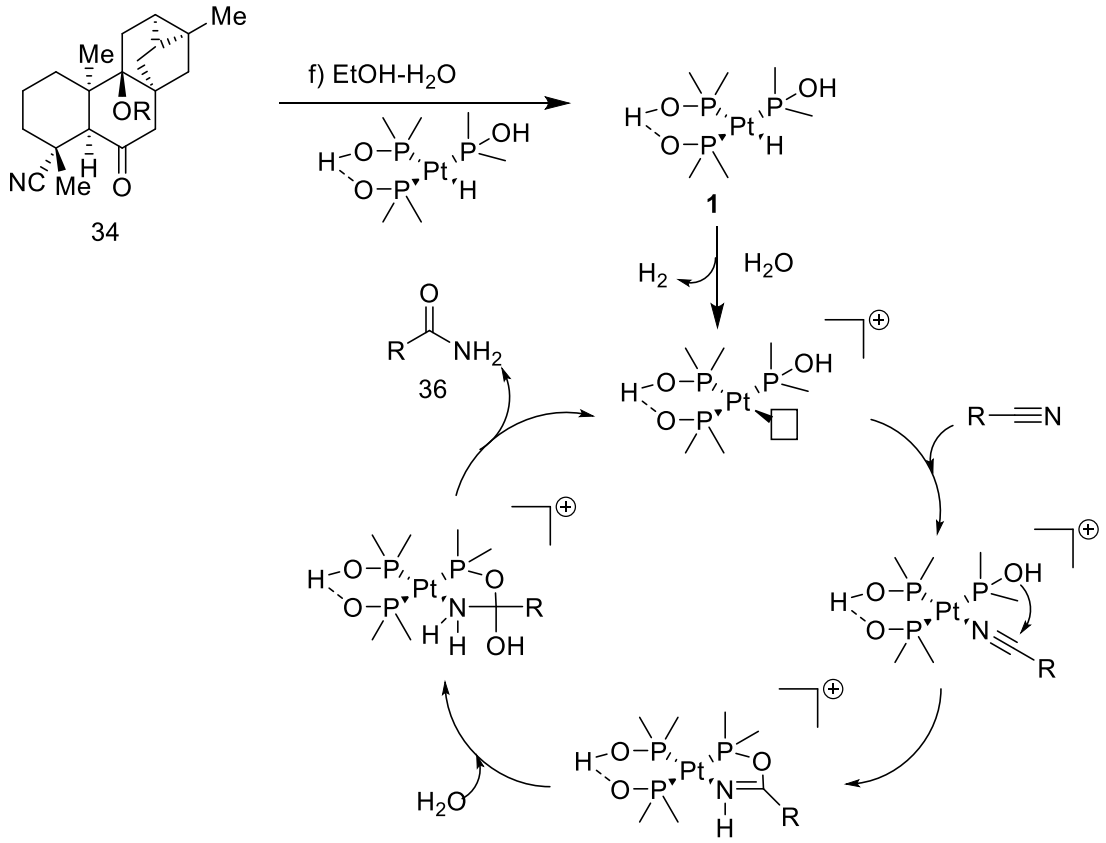


Hydration of the nitrile:



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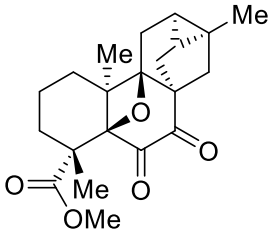

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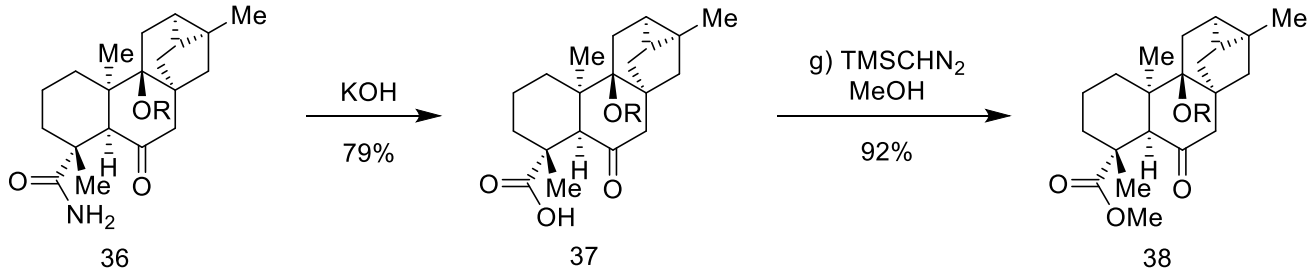

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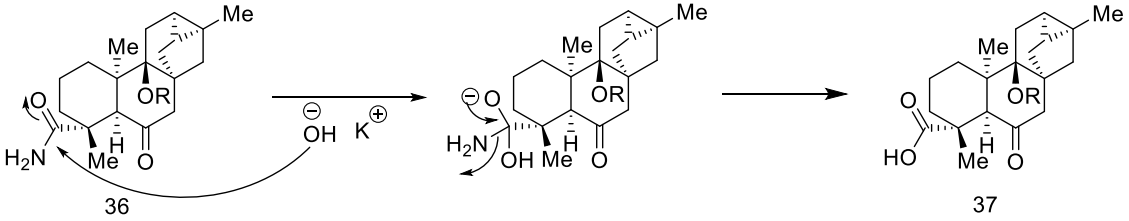
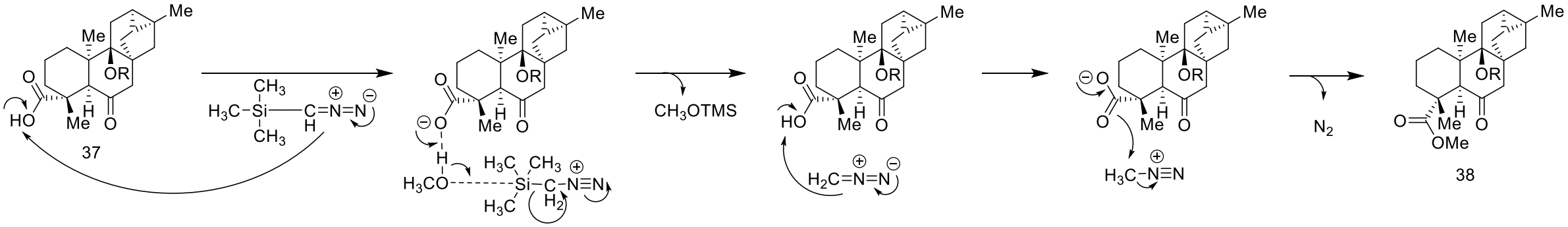


Esterification:



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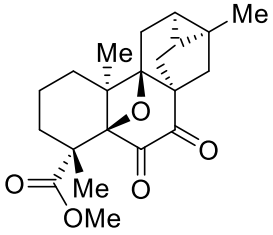

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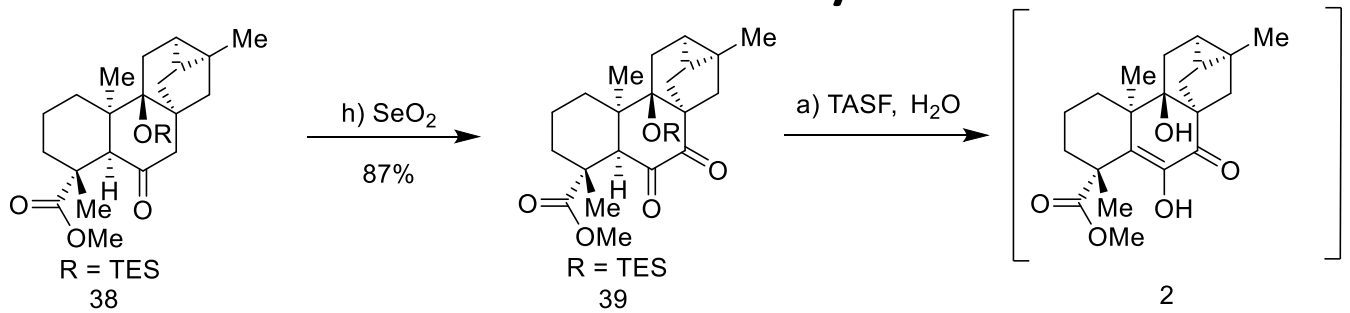
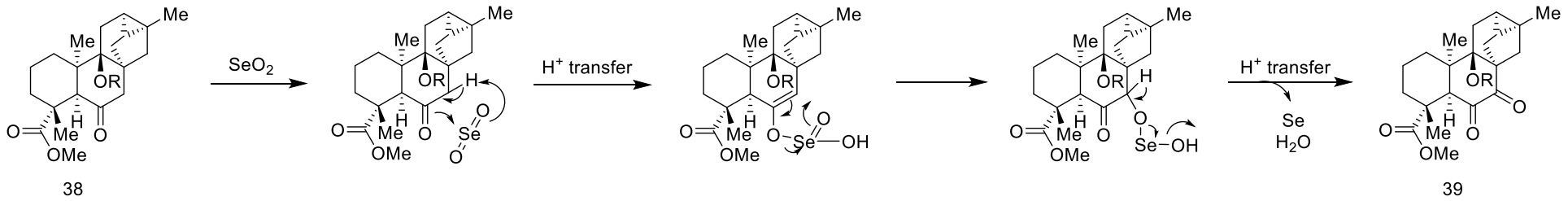
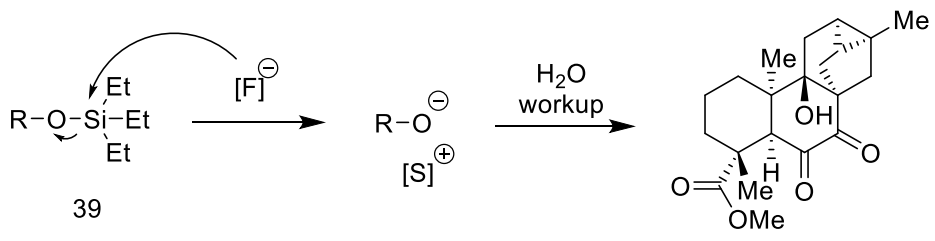


Riley oxidation:



TASF Deprotection:



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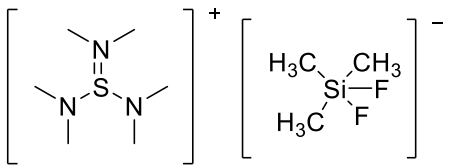

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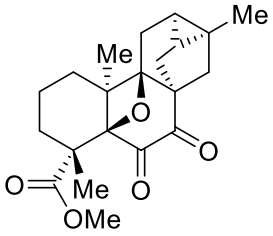
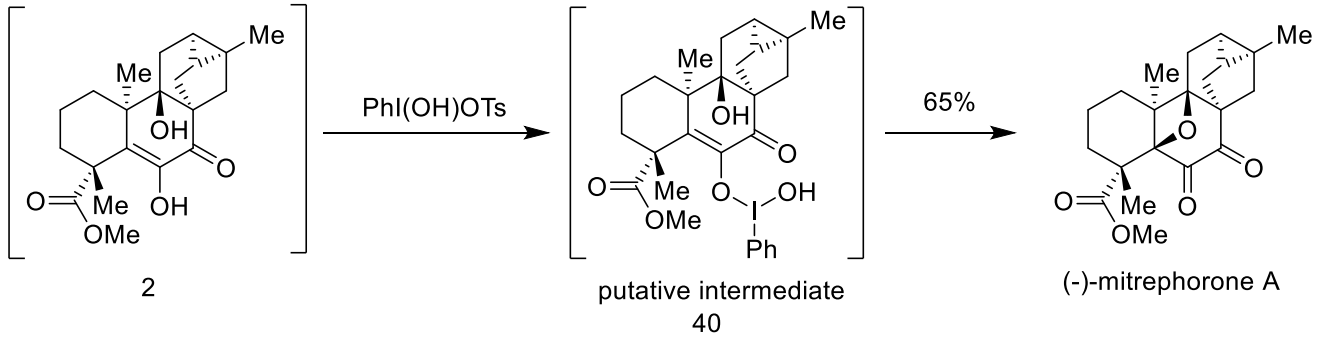


VI. Completion of the Total Synthesis



Oxetane formation using Koser's reagent: